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Effectiveness of daratumumab plus bortezomib, lenalidomide, and dexamethasone (DVRd) versus VRd for transplant-eligible newly diagnosed multiple myeloma

Carlyn Rose Tan[a], Lucio Gordan[b], Joshua Richter [c], Rachel DiLeo[d], Prerna Mewawalla[d], Sarah Larson[e], Faith Davies[f], David Oveisi[g], Niodita Gupta-Werner[h], Rohan Medhekar[h], Xin Yin[h], Annelore Cortoos[h], Marjohn Armoon[h], Philippe Thompson-Leduc[i], Alvi Rahman[i], Anabelle Tardif-Samson[i], Claire Vanden Eynde[i], John Reitan[j], Gary Milkovich[j], Joseph Bubalo[k], Adam Forman[l], Baylee Bryan[m], Douglas Sborov[m], Shuchita Kaila[h] and Saad Usmani[a]

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ABSTRACT

Background: Frontline (1L) treatment for transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM) has shifted from triplet (e.g. bortezomib [V], lenalidomide [R], dexamethasone [d]) to quadruplet (e.g. daratumumab with VRd [DVRd]) regimens, based on improved efficacy demonstrated in pivotal trials. This real-world study compared progression-free survival (PFS) in TE patients with NDMM treated with DVRd plus DR or R maintenance (DVRd-DR/R) versus VRd plus R maintenance (VRd-R).

Methods: Adult TE patients with NDMM who initiated DVRd-DR/R or VRd-R between 1 January 2020 and 30 June 2022 were identified through a retrospective chart review at 10 US sites. PFS was assessed using Kaplan-Meier analyses and propensity score-weighted hazard ratios (HR) were estimated using Cox regression.

Results: Overall, 137 patients received DVRd-DR/R and 86 received VRd-R. Over a median follow-up of 26.7 and 39.8 months among the DVRd-DR/R and VRd-R cohorts, respectively, 11 (9.1%) and 32 (29.7%) patients experienced disease progression or death. Median PFS was not reached in either cohort. DVRd-DR/R versus VRd-R was associated with 63% lower risk of disease progression or death (weighted HR: 0.37, 95% confidence interval: 0.17-0.80, $p = 0.006$).

Conclusion: Findings aligned with pivotal trials, demonstrating the significant PFS benefit of 1L DVRd over VRd and supporting its real-world use for TE NDMM.

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KEYWORDS
Chart review; daratumumab; frontline; multiple myeloma; progression-free survival; real-world; transplant-eligible

1. Introduction

Multiple myeloma (MM) is a hematologic cancer characterized by the accumulation of neoplastic plasma cells in the bone marrow [1,2]. These malignant cells produce monoclonal proteins that are detectable in the blood and urine and can lead to tissue and organ damage [1,2]. Symptoms associated with MM may include hypercalcemia, renal insufficiency, anemia, and bone disease, and patients are typically diagnosed at approximately 70 years of age. Although MM is relatively rare, it remains the second most common hematologic malignancy, accounting for approximately 10% of all hematologic cancer cases [1,3].

Per the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), treatment selection for MM should be guided by multiple factors including patient age, functional status, relapsed/refractory disease status, and, critically, eligibility for hematopoietic stem-cell transplantation (HSCT) [4]. For transplant-eligible (TE) patients with newly diagnosed MM (NDMM), triplet induction therapy with bortezomib, lenalidomide, and dexamethasone (VRd) followed by autologous HSCT and R maintenance therapy had long been the standard of care [5]. However, results from the pivotal phase 3 PERSEUS clinical trial demonstrated that adding the anti-CD38 monoclonal antibody daratumumab (D) to frontline (1L) VRd treatment improved depth of response, minimal residual disease (MRD) negativity rates, and progression-free survival (PFS) with no new safety concerns [6]. In light of these findings, a change in 1L treatment strategy for TE patients has been observed, more specifically a shift from triplet (e.g., VRd) to quadruplet (e.g., DVRd) treatment regimens. Though R remains the standard maintenance therapy for this population, doublet maintenance regimens of carfilzomib-R or DR are recommended for those with high-risk MM [4].

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Article highlights

- Frontline (1L) treatment for transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM) has shifted from triplet (e.g., bortezomib [V], lenalidomide [R], dexamethasone [d]) to quadruplet regimens (e.g., daratumumab plus VRd [DVRd]).
- Superior efficacy of DVRd over VRd has been demonstrated in pivotal trials, however real-world evidence remains limited.
- This retrospective chart review across 10 U.S. sites compared progression-free survival (PFS) in TE NDMM patients who received DVRd followed by DR or R maintenance (DVRd-DR/R) versus VRd followed by R maintenance (VRd-R).
- Kaplan-Meier (KM) analyses were used to estimate PFS and doubly robust Cox regression was used to estimate propensity-score weighted hazard ratios (HR).
- Overall, 137 patients received DVRd-DR/R and 86 received VRd-R; median follow-up was 26.7 and 39.8 months, respectively.
- At 48 months, weighted KM rates for PFS were higher with DVRd-DR/R (85.2%) compared to VRd-R (62.6%).
- DVRd-DR/R was associated with a significantly lower risk of disease progression or death (weighted HR: 0.37; 95% confidence interval 0.17-0.80; $p = 0.006$).
- These real-world findings align with results from the GRIFFIN and PERSEUS trials, supporting the effectiveness of DVRd over VRd as frontline therapy in routine care settings.

While greater efficacy of DVRd over VRd in TE patients with NDMM has been reported in the PERSEUS trial, these results may not fully translate to the real-world setting due to differences in patient characteristics and treatment adherence [7]. For example, the majority of patients who received DVRd induction/consolidation in PERSEUS received maintenance therapy, with DR as the assigned regimen, while real-world patients may receive a wider range of maintenance therapies. Published real-world evidence is limited, highlighting the need to evaluate the comparative effectiveness of DVRd and VRd in routine clinical practice to better inform treatment decision-making. Thus, this retrospective study aimed to compare PFS among TE patients with NDMM who received 1L DVRd induction/consolidation plus DR or R maintenance (DVRd-DR/R) versus VRd induction/consolidation plus R maintenance (VRd-R) in a real-world setting.

2. Patients and methods

2.1. Data source

De-identified patient data were retrieved through a multicenter chart review across 10 clinical sites in the United States (US). Patient charts were abstracted via standardized electronic chart review forms (eCRFs) by an observing clinician or a trained research associate at the site. All patients deemed eligible *(see Patient selection criteria)* were included, except at one site, where a random sample was taken as the target number of patient charts for this site was reached.

This study was reviewed and approved or determined exempt by the applicable Institutional Review Boards (IRBs) at all participating sites, including Memorial Sloan Kettering Cancer Center IRB (23-333), Allegheny Health Network Research Institute IRB (2024-059), NYU Langone Health IRB (i24-00122), Mount Sinai IRB (STUDY-23-01246), UCLA IRB (24-000131), Cedars-Sinai Medical Center IRB (STUDY00003254), Oregon Health & Science University IRB (STUDY00026227), Ascension Health IRB (RMI20230230), University of Utah IRB (00174531), and WCG IRB for participating sites operating under the centralized review process (Florida Cancer Specialists & Research Institute; Exempt Determination D4; WCG Work Order #1-1719660-1). Waivers of informed consent and/or Health Insurance Portability and Accountability Act (HIPAA) authorization were granted or the study was determined exempt, as applicable, as patients were not contacted at any point during the course of this study, and their information was de-identified prior to entry in the eCRFs from respective centers.

2.2. Study design

A retrospective, multi-center, non-interventional, chart review was conducted, which included TE patients with NDMM receiving 1L DVRd followed by DR or R maintenance (the "DVRd-DR/R" cohort) and those who received VRd followed by R maintenance therapy (the "VRd-R" cohort). DR and R maintenance were both examined in those with DVRd induction/consolidation as both maintenance strategies are commonplace in the real world. The index date was defined as the date of initiation of 1L DVRd or VRd between 1 January 2020, and 30 June 2022. The follow-up period was defined as the time from index date to the earliest of: date of death, last available assessment at the site, or date of last data export (i.e., 28 October 2024; see Figure 1).

2.3. Patient selection criteria

Eligible patients with MM were included in the study if they: (i) were at least 18 years of age at first MM diagnosis; (ii) had confirmed NDMM, defined as meeting at least 1 SLiM CRAB Criteria [8] at the time of first MM diagnosis (see Supplemental Table S1); (iii) were TE at initial MM diagnosis as per physician assessment; (iv) initiated either DVRd or VRd as 1L therapy between 1 January 2020, and 30 June 2022; and (v) initiated a 1L maintenance regimen with DR or R thus creating two cohorts: DVRd-DR/R or VRd-R.

Patients were excluded from the study if they: (i) participated in an interventional clinical trial related to MM prior to the index date; (ii) initiated 1L DVRd or VRd treatment more than one year after initial MM diagnosis; (iii) had any invasive malignancy other than MM in the 12 months prior to the index date (except for basal and squamous cell carcinomas and carcinomas in-situ); (iv) received/initiated any NCCN Guidelines-recommended treatment for MM (except corticosteroids) for more than 30 days prior to initial MM diagnosis; or (v) had any prior diagnosis of systemic light-chain amyloidosis.

2.4. Variables

Information abstracted from charts included patient-level demographic characteristics, clinical characteristics, treatment history, and clinical outcomes such as disease progression and death status. Specifically, variables collected included age, sex, race, ethnicity, region of residence, insurance type, Eastern Cooperative Oncology Group (ECOG) performance status,

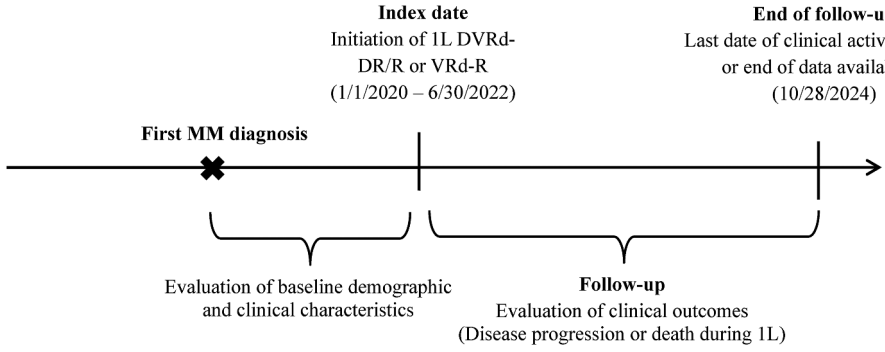

Figure 1. Study design scheme.

Abbreviations: 1L = first line of therapy; DR = daratumumab plus lenalidomide maintenance; DVRd = daratumumab plus bortezomib, lenalidomide, and dexamethasone induction/consolidation; MM = multiple myeloma; R = lenalidomide maintenance; VRd = bortezomib plus lenalidomide, and dexamethasone induction/consolidation.

disease stage based on the International Staging System (ISS) classification or Revised ISS (R-ISS), presence of extramedullary disease, assessment of frailty, cytogenetic risk, and presence of 1q21 amplification or gain. Comorbidities were captured one year prior to or at the time of treatment initiation, including those necessary for the calculation of a modified Charlson Comorbidity Index (CCI; exclusion of lymphoma and leukemia). When data were not available precisely at the time of treatment initiation, the most recent data prior to the index date was used.

2.5. Outcome measure

The primary outcome was PFS during 1L, defined as time from the index date until physician-reported disease progression (event), or death (event), whichever occurred first. Patients without events during 1L were censored at the initiation of next line of therapy, or end of follow-up, whichever occurred first.

2.6. Statistical analysis

Descriptive statistics were used to assess baseline demographic and clinical characteristics, with cohort balance assessed via standardized differences (std. diff.; <10% considered similar) [8,9].

To adjust for differences in baseline characteristics between cohorts, inverse probability of treatment weighting (IPTW) was applied using propensity scores derived from a multivariable logistic regression [10]. Cohort assignment was the dependent variable, with baseline demographic and clinical characteristics used as independent variables. These covariates included age (continuous), male sex, race, ethnicity, type of insurance, region of residence, ECOG ≥1, ISS/R-ISS score of II or III, presence of extramedullary disease (categorical), frailty status, presence of 1q21 amplification or gain, CCI (continuous and categorical), and select comorbidities: diabetes without chronic complications, malignancy, moderate or severe renal disease, chronic obstructive pulmonary disease, hypertension, and obesity. Using this technique, a weight was assigned to each patient, which was normalized and trimmed at the 5th and 95th percentiles to mitigate the statistical impact of outliers. Since weights could have had values greater or less than 1, the effective sample sizes of the weighted cohorts could have been different from those of the unweighted cohorts.

Weighted Kaplan-Meier (KM) curves were used to describe PFS, and a log-rank test was used to compare the rates. Doubly robust Cox proportional hazards models, additionally adjusting for baseline characteristics that remained imbalanced after IPTW, were used to estimate propensity score-weighted hazard ratios (HR) with 95% confidence intervals (CI) for PFS associated with DVRd-DR/R compared with VRd-R.

Since all patients were required to have initiated maintenance, PFS was also assessed from the initiation of maintenance until disease progression or death to explore the robustness of results to potential bias resulting from the selection of patients who survived until maintenance therapy. This analysis also allowed to adjust for a patient's receipt of HSCT prior to the initiation of maintenance.

3. Results

3.1. Sample description

3.1.1. Prior to IPTW

A total of 137 DVRd-DR/R patients and 86 VRd-R patients met the eligibility criteria and were included in the study (Table 1; see Supplementary Table S2 for the distribution of patients by site). Of the DVRd-DR/R cohort, 67 received DR maintenance and 70 received R maintenance. Prior to IPTW, DVRd-DR/R cohort was slightly younger (DVRd-DR/R: 61.7 years, VRd-R: 62.2 years, std. diff.: 4.8%), with fewer females (DVRd-DR/R: 42% female, VRd-R: 51%, std. diff.: 19.3%) and fewer White patients (DVRd-DR/R: 69% White, VRd-R: 76%, std. diff.: 15.6%). DVRd-DR/R cohort had a higher proportion of patients with ISS/R-ISS score of II or III (DVRd-DR/R: 56%, VRd-R: 45%, std. diff.: 20.4%) and slightly higher mean modified CCI (DVRd-DR/R: 0.7, VRd-R: 0.6, std. diff.: 11.1%; Table 2).

The median (interquartile range) lengths of follow-up in the DVRd-DR/R and VRd-R cohorts were 26.7 (22.9–32.6) and 39.8 (29.8–45.1) months, respectively, while the median (interquartile range) durations of 1L treatment (including maintenance therapy) in the DVRd-DR/R and VRd-R cohorts

Table 1. Demographic and baseline characteristics.

	Unweighted cohorts			Weighted cohorts[a]		
	DVRd-DR/R	VRd-R		DVRd-DR/R	VRd-R	
	N = 137	*N* = 86	Std. Diff.	*N* = 115	*N* = 108	Std. Diff.
Age, mean ± SD [median]	61.7 ± 9.6 [63.0]	62.2 ± 8.3 [64.5]	4.8	61.9 ± 8.9 [64.0]	61.9 ± 9.5 [64.0]	0.2
Sex, *n* (%)						
Male	80 (58.4)	42 (48.8)	19.3*	66 (57.2)	61 (56.4)	1.7
Race, *n* (%)						
White	94 (68.6)	65 (75.6)	15.6*	82 (71.2)	79 (73.3)	4.7
Black or African American	14 (10.2)	8 (9.3)	3.1	10 (9.0)	7 (6.6)	9.3
Other[b]	9 (6.6)	4 (4.7)	8.3	7 (5.7)	4 (3.9)	8.4
Unknown	20 (14.6)	9 (10.5)	12.5*	16 (14.1)	18 (16.3)	6.1
Ethnicity, *n* (%)						
Non-Hispanic or Non-Latino	107 (78.1)	72 (83.7)	14.3*	92 (79.7)	85 (79.0)	1.9
Hispanic or Latino	11 (8.0)	8 (9.3)	4.5	8 (7.2)	7 (6.7)	2.0
Other	7 (5.1)	2 (2.3)	14.8*	6 (4.8)	6 (6.0)	5.2
Unknown	12 (8.8)	4 (4.7)	16.5*	9 (8.2)	9 (8.3)	0.4
Region of residence, *n* (%)						
Northeast	74 (54.0)	41 (47.7)	12.7*	57 (49.4)	46 (42.5)	13.9*
West	37 (27.0)	27 (31.4)	9.7	34 (29.8)	37 (34.5)	10.0*
South	18 (13.1)	16 (18.6)	15.0*	19 (16.2)	22 (20.2)	10.3*
Midwest	8 (5.8)	2 (2.3)	17.8*	5 (4.5)	3 (2.8)	9.2
Type of insurance, *n* (%)						
Commercial/private	52 (38.0)	40 (46.5)	17.4*	47 (40.9)	48 (44.9)	8.0
Medicare/Medicare Advantage	37 (27.0)	33 (38.4)	24.4*	36 (31.6)	38 (35.6)	8.4
Medicaid	8 (5.8)	3 (3.5)	11.2*	6 (5.4)	6 (6.0)	2.7
Other[c]	7 (5.1)	2 (2.3)	14.8*	5 (4.0)	3 (2.8)	6.3
Unknown	33 (24.1)	8 (9.3)	40.5*	21 (18.1)	12 (10.7)	21.2*
ECOG performance status, *n* (%)						
0 or unknown	67 (48.9)	46 (53.5)	9.2	56 (48.4)	53 (49.3)	1.8
≥1	70 (51.1)	40 (46.5)	9.2	59 (51.6)	55 (50.7)	1.8
ISS/R-ISS score, *n* (%)						
I or unknown or not reported	61 (44.5)	47 (54.7)	20.4*	53 (46.0)	51 (46.9)	1.8
II or III	76 (55.5)	39 (45.3)	20.4*	62 (54.0)	57 (53.1)	1.8
Extramedullary disease, *n* (%)						
Yes	12 (8.8)	10 (11.6)	9.5	10 (8.6)	9 (8.5)	0.5
No	91 (66.4)	72 (83.7)	40.8*	84 (73.4)	87 (80.4)	16.7*
Unknown	34 (24.8)	4 (4.7)	59.4*	21 (18.0)	12 (11.1)	19.6*
Frailty assessment at clinic, *n* (%)						
Fit	53 (38.7)	32 (37.2)	3.0	47 (40.5)	47 (43.8)	6.5
Intermediate fitness	5 (3.6)	3 (3.5)	0.9	5 (3.9)	5 (4.8)	4.5
Frail	2 (1.5)	2 (2.3)	6.4	2 (1.8)	2 (1.7)	0.9
Unknown	77 (56.2)	49 (57.0)	1.6	62 (53.7)	54 (49.7)	8.0
High cytogenetic risk[d], *n* (%)	14 (10.2)	7 (8.1)	7.2	11 (9.3)	11 (10.2)	2.8
1q21 gain or amplification, n (%)						
Yes	37 (27.0)	18 (20.9)	14.3*	29 (25.4)	28 (25.9)	1.0
No	93 (67.9)	58 (67.4)	0.9	79 (68.2)	72 (66.5)	3.6
Unknown	7 (5.1)	10 (11.6)	23.7*	7 (6.3)	8 (7.6)	5.0

*Std. Diff. ≥ 10%.

[a]Weights were estimated using a multivariable logistic regression model with the following baseline covariates: age (continuous), male, race, ethnicity, type of insurance, region of residence, ECOG score of 1 or higher, ISS/R-ISS score of 1 or unknown or not reported, extramedullary disease (categorical), frailty, presence of 1q21 amplification or gain, CCI score (continuous and categorical) and selected comorbidities: diabetes without chronic complications, malignancy, moderate or severe renal disease, chronic obstructive pulmonary disease, hypertension and obesity. Weights were trimmed at the 5thand 95thpercentiles. The number of patients reported in this weighted population represents the sum of weights for the corresponding patients, rounded to the nearest integer. The proportions displayed were calculated prior to the rounding and may be slightly different than if they were calculated based on rounded numbers.

[b]Includes Asian, Hispanic or Latino, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native.

[c]Includes dual eligible, military and other. Dual eligible was defined as having both Medicare plus Medicaid insurance coverage. Military included Veterans Affairs and active military.

[d]Patients with markers in del17 or any two of the following abnormalities together: i) t[4,14], t[14,16], or t[14,20] abnormalities; ii) 1q21 gain or amplification.

Abbreviations: DR = daratumumab plus lenalidomide maintenance; DVRd = daratumumab plus bortezomib, lenalidomide, and dexamethasone induction/consolidation; ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; MM = multiple myeloma; R = lenalidomide maintenance; SD = standard deviation; Std. Diff. = standardized difference; VRd = bortezomib plus lenalidomide and dexamethasone induction/consolidation.

were 26.3 (22.4–32.6) and 30.9 (22.6–40.8) months, respectively. The median (interquartile range) duration of induction therapy was 6.4 (4.7–8.0) months in the DVRd-DR/R cohort and 5.6 (4.5–7.3) months in the VRd-R cohort; 75.2% and 90.7% of patients, respectively, received an HSCT during 1L therapy, and 9.5% and 2.3% received consolidation therapy. Among the 34 patients (24.8%) who did not receive an upfront HSCT in the DVRd-DR/R cohort, 5 declined the procedure and 29 deferred the HSCT. Common reasons for deferral included proceeding directly to maintenance therapy (55.2%), the intent to sustain or deepen response prior to transplant (6.9%), the presence of comorbidities (6.9%), patient choice (6.9%), and the inability to collect stem cells (6.9%). Among the 8 patients (9.3%) who did not receive an

Table 2. Patient comorbidities.

	Unweighted cohorts			Weighted cohorts[a]		
	DVRd-DR/R	VRd-R		DVRd-DR/R	VRd-R	
	N = 137	*N* = 86	Std. Diff.	*N* = 115	*N* = 108	Std. Diff.
Modified CCI[b], mean ± SD [median]	**0.7 ± 1.1 [0.0]**	**0.6 ± 1.1 [0.0]**	**11.1***	**0.6 ± 0.9 [0.0]**	**0.5 ± 1.0 [0.0]**	**14.3***
0, *n* (%)	89 (65.0)	57 (66.3)	2.8	78 (67.6)	79 (72.8)	11.3*
1, *n* (%)	16 (11.7)	15 (17.4)	16.4*	14 (12.6)	14 (12.7)	0.4
2, *n* (%)	22 (16.1)	13 (15.1)	2.6	17 (15.1)	15 (13.9)	3.2
≥3, *n* (%)	10 (7.3)	1 (1.2)	30.9*	5 (4.8)	1 (0.6)	26.1*
CCI comorbidities, *n* (%)	**91 (66.4)**	**64 (74.4)**	**17.6***	**77 (67.1)**	**73 (67.2)**	**0.2**
Diabetes without chronic complications	16 (11.7)	8 (9.3)	7.8	13 (11.3)	9 (8.2)	10.4*
Malignancy	13 (9.5)	6 (7.0)	9.2	9 (7.7)	5 (4.6)	13.1*
Moderate or severe renal disease	12 (8.8)	3 (3.5)	22.1*	8 (7.1)	6 (5.7)	5.9
Diabetes with chronic complications	6 (4.4)	2 (2.3)	11.4*	4 (3.7)	1 (1.3)	15.0*
Chronic obstructive pulmonary disease[c]	3 (2.2)	5 (5.8)	18.6*	3 (2.5)	4 (3.3)	4.5
Congestive heart failure	2 (1.5)	3 (3.5)	13.1*	2 (1.9)	3 (3.1)	7.6
Peptic ulcer disease	2 (1.5)	2 (2.3)	6.4	1 (1.2)	2 (1.5)	3.1
Rheumatological disease	2 (1.5)	0 (0.0)	17.2*	1 (1.0)	0 (0.0)	14.5*
Peripheral vascular disease	1 (0.7)	1 (1.2)	4.5	1 (0.5)	1 (0.6)	1.6
Cerebrovascular disease	1 (0.7)	1 (1.2)	4.5	1 (1.1)	1 (0.8)	3.2
AIDS / HIV	1 (0.7)	0 (0.0)	12.1*	1 (0.5)	0 (0.0)	9.8
Mild liver disease	0 (0.0)	1 (1.2)	15.3*	0 (0.0)	1 (1.1)	15.0*
Metastatic solid tumor	0 (0.0)	1 (1.2)	15.3*	0 (0.0)	1 (0.6)	10.8*
Myocardial infarction	0 (0.0)	0 (0.0)	0.0	0 (0.0)	0 (0.0)	0.0
Hemiplegia or paraplegia	0 (0.0)	0 (0.0)	0.0	0 (0.0)	0 (0.0)	0.0
Moderate or severe liver disease	0 (0.0)	0 (0.0)	0.0	0 (0.0)	0 (0.0)	0.0
Dementia	0 (0.0)	0 (0.0)	0.0	0 (0.0)	0 (0.0)	0.0
Other comorbidities, *n* (%)						
Hypertension	55 (40.1)	41 (47.7)	15.2*	48 (42.1)	46 (42.7)	1.2
Obesity	23 (16.8)	19 (22.1)	13.4*	22 (19.1)	22 (20.2)	2.7
Peripheral neuropathy	8 (5.8)	5 (5.8)	0.1	9 (7.6)	5 (4.5)	13.0*
Coronary heart disease	7 (5.1)	3 (3.5)	8.0	5 (4.1)	4 (3.3)	4.3

*Std. Diff. ≥10% .

[a]Weights were estimated using a multivariable logistic regression model with the following baseline covariates: age (continuous), male, race, ethnicity, type of insurance, region of residence, ECOG score of 1 or higher, ISS/R-ISS score of 1 or unknown or not reported, extramedullary disease (categorical), frailty, presence of 1q21 amplification or gain, CCI score (continuous and categorical) and selected comorbidities: diabetes without chronic complications, malignancy, moderate or severe renal disease, chronic obstructive pulmonary disease, hypertension and obesity. Weights were trimmed at the 5thand 95thpercentiles. The number of patients reported in this weighted population represents the sum of weights for the corresponding patients, rounded to the nearest integer. The proportions displayed were calculated prior to the rounding and may be slightly different than if they were calculated based on rounded numbers.

[b]Excludes lymphoma and leukemia.

[c]Includes asthma.

Abbreviations: AIDS = acquired immunodeficiency syndrome; CCI = Charlson comorbidity index; DR = daratumumab plus lenalidomide maintenance; DVRd = daratumumab plus bortezomib, lenalidomide, and dexamethasone induction/consolidation; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; ISS/R-ISS = International Staging System / Revised-ISS; MM = multiple myeloma; R = lenalidomide maintenance; SD = standard deviation; Std. Diff. = standardized difference; VRd = bortezomib plus lenalidomide and dexamethasone induction/consolidation.

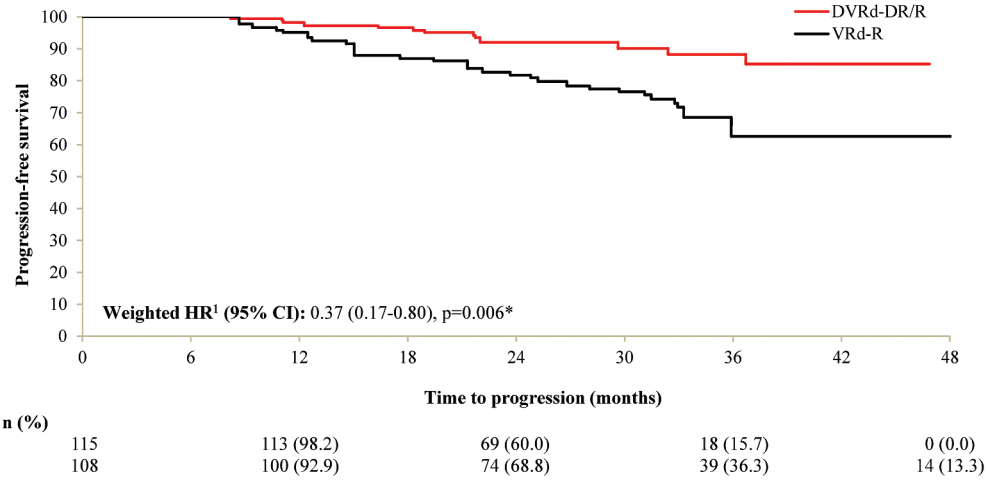

Figure 2. Weighted progression-free survival, assessed from the start of induction.

*Indicates statistical significance at $p < 0.05$.

[1]In addition to the IPTW adjustment, the doubly robust Cox model adjusted for region of residence, type of insurance, presence of extramedullary disease, presence of plasmacytomas, CCI score (continuous and categorical), diabetes without chronic complications, malignancy, and peripheral neuropathy.

Abbreviations: CCI = Charlson comorbidity index; CI = confidence interval; DR = daratumumab plus lenalidomide maintenance; DVRd = daratumumab plus bortezomib, lenalidomide, and dexamethasone induction/consolidation; HR = hazard ratio; IPTW = inverse probability of treatment weighting; R = lenalidomide maintenance; VRd = bortezomib plus lenalidomide and dexamethasone induction/consolidation.

HSCT in the VRd-R cohort, 6 declined the procedure and 2 deferred the HSCT.

3.1.2. Following IPTW

After IPTW, the sum of the weights assigned to patients in the DVRd-DR/R cohort represented approximately 115 patients, and 108 patients in the VRd-R cohort (see Supplementary Table S2 for the distribution of patients by site). Baseline characteristics were well balanced between cohorts (standardized differences <10%), with small differences remaining in the region of residence, type of insurance, presence of extramedullary disease, presence of plasmacytomas, CCI score, diabetes without chronic complications, malignancy, and peripheral neuropathy (Tables 1 and 2). These variables were thus added to the list of regressors for additional adjustment in the doubly robust Cox proportional hazards models as described in the *Methods* section.

3.2. Comparison of PFS

Overall, 11 (9.1%) DVRd-DR/R patients and 32 (29.7%) VRd-R patients experienced disease progression or death during 1L. Median time to progression or death was not reached in either cohort.

Weighted KM rates indicated lower rates of disease progression or death in the DVRd-DR/R cohort compared with the VRd-R cohort (Figure 2). At 48 months, the KM rate was 85.2% among DVRd-DR/R patients and 62.6% among VRd-R patients (log-rank test: $p = 0.006$). There was a 63% lower risk of disease progression or death among DVRd-DR/R patients compared to VRd-R (HR: 0.37, 95% CI: 0.17-0.80, $p = 0.006$). Findings were consistent when looking at the PFS from the initiation of maintenance instead of the index date (HR: 0.30, 95% CI: 0.13–0.70, $p = 0.005$; Figure 3).

4. Discussion

In this real-world multi-center chart review study, TE patients with NDMM treated with 1L DVRd induction/consolidation followed by DR or R maintenance had a 63% lower risk of disease progression or death compared to those treated with 1L VRd followed by R maintenance. These findings are consistent with those of the pivotal phase 2 GRIFFIN and phase 3 PERSEUS clinical trials, providing additional evidence for the superiority of the daratumumab-based quadruplet regimen DVRd over VRd for TE patients with NDMM in the real world.

Prior to this analysis, only one real-world study had evaluated 1L DVRd versus VRd among TE patients with NDMM in the US. In that study, data were obtained from the Emory University Winship Cancer Institute myeloma database and through manual chart abstraction. Maintenance therapy was informed by patients' cytogenetic risk, where those with standard risk received R monotherapy, while high-risk patients received a combination of a proteasome inhibitor and an immunomodulatory agent post-transplant [11]. Consistent with the findings of the present analysis, DVRd was associated with a 62% lower risk of disease progression or death compared to VRd (HR: 0.38, 95% CI: 0.18–0.85, $p < 0.017$) [11]. Nonetheless, the current study addresses several methodological limitations noted in the previous analysis. First, while the comparison in the previous study was based on sequential cohorts of 326 patients treated with VRd (January 2007 to August 2016) or DVRd (April 2018 to August 2022), all patients in the present analysis initiated 1L DVRd or VRd treatment

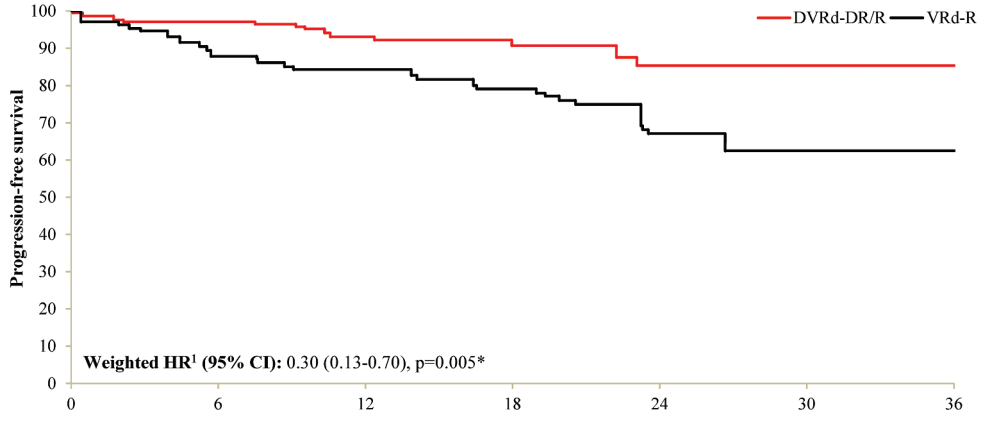

Figure 3. Weighted progression-free survival, assessed from the start of maintenance therapy.

*Indicates statistical significance at $p < 0.05$.

[1]In addition to the IPTW adjustment (which included receipt of stem cell transplant prior to maintenance in the calculation of the weight), the doubly robust Cox model adjusted for race, weight, BMI, type of insurance, ISS/R-ISS score, measurable disease type, presence of extramedullary disease, frailty, high risk cytogenetic prognosis, absence of plasmacytomas, CCI, receipt of stem cell transplant, diabetes without chronic complications, malignancy, chronic obstructive pulmonary disease, and congestive heart failure.

Abbreviations: BMI = body mass index; CCI = Charlson comorbidity index; CI = confidence interval; DR = daratumumab plus lenalidomide maintenance; DVRd = daratumumab plus bortezomib, lenalidomide, and dexamethasone induction/consolidation; HR = hazard ratio; IPTW = inverse probability of treatment weighting; ISS/R-ISS = International Staging System / Revised-ISS; R = lenalidomide maintenance; VRd = bortezomib plus lenalidomide and dexamethasone induction/consolidation.

within the same period (January 2020 to June 2022), reducing potential temporal bias. Second, statistical analyses in the previous study were not adjusted for differences in baseline characteristics, whereas the current study employed doubly robust IPTW to improve comparability between treatment groups. Taken together, these methodological improvements strengthen the validity of the present findings and build on previous real-world evidence, providing further support for the effectiveness of DVRd in TE patients with NDMM.

Key differences exist between the controlled clinical trial environment and the complexity of real-world clinical practice. Indeed, in the GRIFFIN and PERSEUS trials, patients in the DVRd arm received an HSCT and DR maintenance per protocol [6,12]. In this real-world study, patients with DVRd induction/consolidation did not all receive an HSCT and may have received a variety of maintenance therapies, depending on initial treatment outcomes, of which DR and R were most common. Nevertheless, our findings are similar to those of the two pivotal trials. In the final analysis of the open-label, randomized, controlled, phase 2 GRIFFIN trial, which was conducted after all patients had either completed >1 year of follow-up post-treatment, had died, or had withdrawn from the trial, TE patients with NDMM who received 1L DVRd had a 55% lower risk of disease progression or death compared to those treated with VRd (HR: 0.45, 95% CI: 0.21–0.95, $p = 0.032$) [13]. The 48-month PFS was 87.2% and 70.0% for DVRd and VRd, respectively [13]. Similarly, the open-label, multi-center, phase 3 PERSEUS trial evaluated the efficacy of 1L DVRd and VRd in TE patients with NDMM, reporting a 57% lower risk of disease progression or death with DVRd versus VRd treatment (HR: 0.43, 95% CI: 0.30–0.59, $p < 0.001$) and a 48-month PFS of 84.3% and 67.7%, respectively [6]. Importantly, the HR for disease progression or death associated with 1L DVRd versus VRd identified in the present study falls within the CIs observed in both the GRIFFIN and PERSEUS trials, aligning with and confirming the applicability of prior trial findings to the real-world TE NDMM population.

While this study reinforced the superiority of 1L DVRd over VRd for TE patients with NDMM, sample size constraints limited the comparison of outcomes between patients who received DR maintenance with those who received R maintenance. Nevertheless, in the PERSEUS trial, DR maintenance therapy was administered to patients in the DVRd cohort and, when compared to VRd followed by R maintenance therapy, was associated with higher rates of sustained MRD negativity for ≥12 months (DVRd-DR: 64.8%, VRd-R: 29.7%) [6]. This was supported by findings from the phase 3 AURIGA clinical trial, which included patients who received induction therapy and HSCT and achieved at least very good or partial response. In that trial, compared to R maintenance, those with DR maintenance achieved significantly higher MRD negativity (odds ratio: 4.51, 95% CI: 2.37–8.57, $p < 0.001$) and improved PFS (HR: 0.53, 95% CI: 0.29–0.97, $p < 0.05$) [14]. Given the PERSEUS and AURIGA trial results and the inclusion of DVRd in the NCCN Guidelines Recommendations as a preferred primary therapy [4], future real-world studies evaluating DR compared with R maintenance are warranted.

The conclusions of this study were strengthened using robust methodological techniques. Unlike analyses based solely on electronic medical records (EMR) data, conducting a chart review enabled the collection of rich clinical data not typically available in EMR (e.g., disease progression, transplant-eligibility), adjudication of inconsistencies, execution of quality control checks, and confirmation of missingness across data sources. Additionally, the use of doubly robust IPTW allowed for a statistical comparative assessment of real-world outcomes that account for baseline differences between treatment cohorts and generation of effect estimates that are robust to misspecification of either the treatment model (i.e., propensity score model) or the outcome model (i.e., multivariable Cox regression).

4.1. Limitations

Study findings should be interpreted in light of some limitations. Data analysis was restricted to the information available from patient EMRs and medical charts, which do not constitute a closed system. Though physician notes often include care received outside of sites, some services received may not have been fully captured. Further, since data were obtained from multiple sites, differences in the level of missingness for some data elements across sites may have existed. As this was a non-randomized, observational chart review study, confounding by indication is an inherent limitation. Treatment decisions, including the choice to initiate DVRd or VRd as well as subsequent maintenance strategies, were made at the discretion of treating physicians and may have been influenced by patient characteristics, physician preferences, and institutional practices. To mitigate the impact of measured confounding, IPTW was used to balance baseline characteristics between treatment cohorts. However, unmeasured confounders not captured within the eCRF, including institution-specific protocols, may have led to residual confounding. In addition, variability in dosing and scheduling across institutions, reflecting real-world clinical practice and physician discretion, may have introduced heterogeneity in treatment exposure. Differences in follow-up duration between cohorts should be considered; however, the median treatment duration was similar between cohorts, PFS analyses were censored at the end of 1L treatment, and KM analyses accounted for variable follow-up and censoring, collectively minimizing the impact of differential follow-up on study findings. In terms of comparability with the pivotal clinical trials, some limitations may exist due to differences in 1L treatment patterns in the real world, including lower rates of consolidation and longer length of induction therapy. All patients received maintenance therapy, and results may not be applicable to those who experience earlier disease progression. Moreover, while the sample size for comparing DVRd and VRd cohorts was sufficient, it limited the ability to conduct detailed subgroup analyses, assess institution-level prescribing patterns, or adjust for center-specific effects. In particular, the number of DVRd recipients with DR and with R maintenance was not sufficient for a robust comparison. As all patients were required to be TE at initial MM diagnosis, study findings may not be generalizable to other patient populations. Finally, because safety data, including the use of infection prevention protocols, were not captured in this chart review, detailed analyses of infection-

related complications could not be provided. Thus, study findings should be interpreted with appropriate consideration of known safety profiles, including the risk of infection.

5. Conclusion

Findings from this multi-center chart review demonstrated that 1L treatment with the daratumumab-based quadruplet regimen DVRd followed by either DR or R maintenance was associated with a significantly lower risk of disease progression or death compared to VRd among TE patients with NDMM. These real-world findings are consistent with those of the pivotal GRIFFIN and PERSEUS trials, highlighting the clinical effectiveness of DVRd in real-world clinical practice and underscoring its superiority over VRd as 1L treatment in this patient population. Importantly, this study extends evidence from these pivotal trials by evaluating outcomes in routine clinical practice across multiple institutions, where treatment patterns, including use of HSCT and maintenance strategies, may vary. Overall, these findings support the growing body of evidence favoring DVRd as a preferred 1L treatment option for TE patients with NDMM. Future real-world studies with larger sample sizes and longer follow-up are warranted to better characterize long-term outcomes, safety, and the comparative effectiveness of maintenance strategies.

Author contributions

CRediT: **Carlyn Rose Tan:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Lucio Gordan:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Joshua Richter:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Rachel DiLeo:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Prerna Mewawalla:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Sarah Larson:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Faith Davies:** Conceptualization, Investigation, Methodology, Writing – review & editing; **David Oveisi:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Niodita Gupta-Werner:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing; **Rohan Medhekar:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing; **Xin Yin:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing; **Annelore Cortoos:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing; **Marjohn Armoon:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing; **Philippe Thompson-Leduc:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; **Alvi Rahman:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; **Anabelle Tardif-Samson:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; **Claire Vanden Eynde:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; **John Reitan:** Data curation, Investigation, Validation, Writing – review & editing; **Gary Milkovich:** Data curation, Investigation, Validation, Writing – review & editing; **Joseph Bubalo:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Adam Forman:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Baylee Bryan:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Douglas Sborov:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Shuchita Kaila:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing; **Saad Usmani:** Conceptualization, Investigation, Methodology, Writing – review & editing.

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Ethical conduct of research

This study was reviewed and approved or determined exempt by the applicable IRBs at all participating sites, including Memorial Sloan Kettering Cancer Center IRB (23-333), Allegheny Health Network Research Institute IRB (2024-059), NYU Langone Health IRB (i24-00122), Mount Sinai IRB (STUDY-23-01246), UCLA IRB (24-000131), Cedars-Sinai Medical Center IRB (STUDY00003254), Oregon Health & Science University IRB (STUDY00026227), Ascension Health IRB (RMI20230230), University of Utah IRB (00174531), and WCG IRB for participating sites operating under the centralized review process (Florida Cancer Specialists & Research Institute; Exempt Determination D4; WCG Work Order #1-1719660-1). Waivers of informed consent and/or HIPAA authorization were granted or the study was determined exempt, as applicable, as patients were not contacted at any point during the course of this study, and their information was de-identified prior to entry in the eCRFs from respective centers.

Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Previous presentations

Parts of the material in this manuscript were presented as poster presentations at the 66th American Society of Hematology (ASH) Annual Meeting held December 7–10, 2024, in San Diego, CA and at the 22nd International Myeloma Society Annual Meeting held September 17–20 in Toronto, Canada.

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